REMARKS

I. Introduction

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claim 18 has been canceled, without prejudice or disclaimer thereof, and claims 1-3, 13, 17, 19, 35, 39, 44, 45, 56, 60, 61, 62, 70, and 78 are currently being amended.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier in the Listing of the Claims beginning on page 2 of this communication.

Claims 1, 39, and 60 have been amended to define the size of the particles of fluticasone or a salt thereof as less than about 900 nm, wherein 50% of the particles are less than 900 nm. See e.g., paragraphs [0110] and [0112] of the application. Dependent claims 2, 44, and 61 have been amended to define the largest particle size as "less than about 800 nm." Claims 3, 19, 45, 62, and 70 have been amended to change the dependency of the claims; claims 13, 35, 56, and 78 have been amended to recite generic chemical names for the trademarks POLYQUAT 10, MIRAPOL, and ALKAQUAT; and claim 17 has been amended to incorporate the subject matter of canceled claim 18.

Because the foregoing amendments do not introduce new matter, entry thereof by the Examiner is respectfully requested. After amending the claims as set forth above, claims 1-81 are pending in this application.

II. Response to Issues Raised by Examiner in the Office Action

A. Claim Objections

Claim 3 is objected to as allegedly improper for depending from itself. Claim 3 has been amended to depend from claim 1.

The use of the trademarks Polyquat 10, Mirapol, and Alkaquat in claims 13, 35, 56, and 78 was noted by the Examiner. As amended herein, these trademarks are accompanied by their generic terminology, pursuant to the Examiner's request.

Claim 70 is objected to for stating that it depends from "the method of claim 1." However, claim 1 is directed to a composition rather than a method. As amended herein claim 70 depends from the method of claim 60.

B. Claim Rejections – 35 USC § 112, Second Paragraph

Claims 17, 20, and 21 are rejected under 35 USC § 112, second paragraph, as being indefinite for alleged insufficient antecedent basis for the term "fluticasone particles" in claim 17. As amended herein, the composition of claim 17 has been further defined as comprising fluticasone particles.

This rejection has been rendered moot by amendments to the claims. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

C. Claim Rejections – 35 USC § 102(e)

Claims 1, 2, 4, 5, 10, 12, 39-41, 44, 48, 53, 54, and 70 were rejected under 35 USC § 102(e) as being allegedly unpatentable over Wertz et al. (US 2003/0185869). Office Action at pages 3-4. Applicants respectfully traverse this ground for rejection.

Submitted herewith is a Declaration under 37 CFR 1.132 by the inventors of the present case wherein they state,

> To the extent that the '514 application [Wertz et al., US 2003/0185869] may teach or suggest the invention claimed in the captioned application, that information was derived from the inventors of the captioned application and was not invented by the inventive entity of the '514 application.

Thus, the disclosure of the Wertz reference relevant to the claimed invention is derived from the inventors of the present application. Therefore, to the extent that this reference applies to the formulations of the present application, this reference is not available as prior art.

Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

D. Claim Rejections – 35 USC § 103

Claims 1-11, 16-33, 38-54, 59-76, and 81 were rejected under 35 USC § 103(a) as being allegedly unpatentable over Karlsson et al. (US 2002/0065256) ("Karlsson"). Office Action at pages 4-5. Applicants respectfully traverse this ground for rejection.

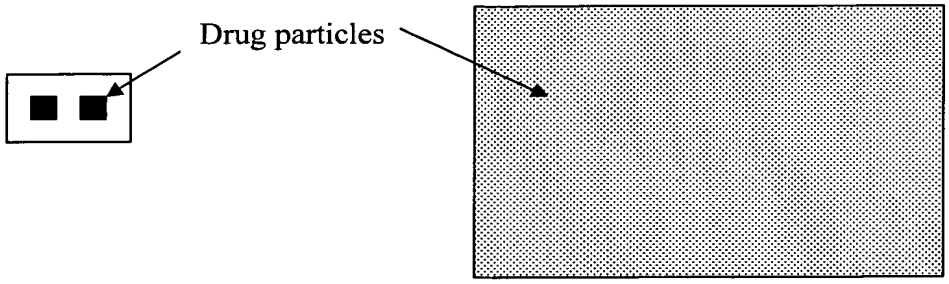
1. Summary of Karlsson

Contrary to the Examiner's assertion, Karlsson does not teach or suggest the claimed nanoparticulate fluticasone formulations (claims 1-38) or methods of making such formulations (claims 39-59), or methods of treatment using such compositions (claims 60-81). Karlsson is directed to a process for sterilizing a powdered form of a glucocorticosteroid and compositions made using such a process. The glucocorticosteroid of Karlsson is present in a *micronized* powder. *See* paragraph 0017 of Karlsson, which notes that the glucocorticosteroid is "in the form of finely divided particles having a mass median diameter of less than 10 μm, more preferably less than 5 μm . . . [or] less than 1.0 μm." Karlsson at paragraph 0042. The smallest particle size distribution taught by Karlsson is wherein 50% of the drug particles have a size of less than 1 micron. See paragraph [0017] of Karlsson, which refers to a composition "having a mass median diameter of less than 1.0 micron.".

a. Applicant's Claimed Fluticasone Particle Sizes of the Invention of Claims 1-16, 39-45, 47-59, 60-62, and 64-81, is Distinguishable from that of Karlsson

Claims 1-16 are drawn to nanoparticulate compositions, claims 39-45 and 47-59 are directed to methods of making such compositions, and claims 60-62 and 64-81 are directed to methods of treatment using such compositions. In contrast to Karlsson, the compositions and methods of the invention encompass a fluticasone composition in which 90% of the particles have a size of less than about 900 nm. In contrast, Karlsson is directed to fluticasone compositions having much larger particle sizes: the smallest fluticasone particle size distribution taught by Karlsson is a composition in which 50% of the particles have a size of less than 1 micron.

The difference in the particle size distribution taught by Karlsson and that encompassed by the claimed invention is not inconsequential. This is because smaller fluticasone particle sizes result in a greater number of fluticasone particles per unit dose. For drugs like fluticasone that act topically, the increased number of particles per unit dose allows larger physiological surface areas to be treated (see diagram below).



Large particles cover small surface area. Finely divided particles cover large surface area.

A decrease in particle size from that disclosed by Karlsson (smallest particle size of 50% less than 1 micron) as compared to that claimed by Applicant's (largest particle size of 50% less than about 900 nm) results in a *minimum* increase of about 37% in the number of drug particles per unit dose. Specifically, for a sample of mass = M, the number of particles x mass of each particle = total mass:

$$M = N\ 4/3\pi r^3\rho.$$

Where N = number of particles, $4/3\pi r^3$ = volume of a particle, ρ = density. Units could be cm^3 per particle for volume, g/cm^3 for density, so total mass is in grams. For two possible particle sizes r_1 and r_2, the equations are:

$$M = N_1\ 4/3\pi r_1^3\rho \text{ and } M = N_2\ 4/3\pi r_2^3\rho$$

Setting these equal to each other, $N_1\ 4/3\pi r_1^3\rho = N_2\ 4/3\pi r_2^3$ This can be rearranged to $N_1/N_2 = 4/3\pi r_2^3 / 4/3\pi r_1^3\rho$ which reduces to $N_1/N_2 = r_2^3 / r_1^3$. Thus, if r_2 = 500 nm and r_1 = 450 nm, N_1/N_2 = 1.37 (a 37% increase in the number of particles in going from d = 1000 nm to d = 900 nm).

Fluticasone does not act systemically; the drug is delivered locally to, for example, the upper airways. A dosage form comprising a greater number of drug particles per unit dose

results in more extensive distribution of the drug dose over the relevant physiological surface area, along with faster dissolution and faster onset of activity. This is particularly desirable for a drug, such as fluticasone, intended to treat respiratory conditions.

Karlsson does not provide any motivation to make a composition having a drug particle size which is smaller than 50% less than 1 micron, as Karlsson is in fact directed to compositions having *much larger* particle sizes. The drug particle size of "50% less than 1 micron" is at the bottom of the particle size range given by Karlsson, with the largest drug particle sizes extending up to 20 microns (paragraph [0042] of Karlsson). Moreover, Karlsson does not teach *how* one of ordinary skill in the art would modify the teaching of Karlsson to obtain the smaller particle size of the claimed invention, with any reasonable expectation of success. For at least these reasons, withdrawal of this ground for rejection is respectfully requested.

b. The Invention of Claims 17, 19-38, 46, and 62, Directed to Sterile Filterable Fluticasone Compositions and Methods of Making and Using the Same

Claims 17 and 19-38 are directed to sterile filterable fluticasone compositions, claim 46 is directed to methods of making such compositions, and claim 62 is directed to methods of treatment using such compositions. This subject matter is not taught or suggested by Karlsson.

Karlsson does not teach or suggest fluticasone compositions having a fluticasone particle size small enough to facilitate sterile filtration, which is required by claims 17, 19-38, 46, and 62.

The Examiner asserts that paragraph [0044] of Karlsson teaches "that a suspension containing the active agent and additional ingredients can be produced by sterile filtration" (Office Action, page 5). This is in fact, a mischaracterization of what is taught by paragraph [0044], which states that "[a]ll components, other than glucocorticosteroids, can be produced by sterile filtration of their aqueous solutions" (emphasis added). Indeed, filtration of all component of a suspension except the glucocorticosteroid is consistent with the emphasis of the Karlsson reference, which is dry heat sterilization of glucocorticosteroids. Furthermore, the Karlsson reference does not teach any examples of glucocorticosteroid particles that are small enough (i.e., less than 0.2 μm) to be sterile filtered. Indeed, one of skill in the art would readily recognize that

the sterile filtration of a suspension made by the teachings of the Karlsson reference would result in the loss of the bulk of the glucocorticosteroid because the majority of the glucocorticosteroid particles would be greater than 0.2 μm.

Thus, Karlsson does not teach or suggest sterile filterable fluticasone compositions, or methods of making and using such compositions, as recited in claims 17, 19-38, 46, and 62. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Conclusion

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date August 7, 2006

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